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HEAVY-ION IMAGING APPLIED TO MEDICINE

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Abstract

Heavy particle radiography is a newly developed noninvasive low dose imaging procedure with increased resolution of minute density differences in soft tissues of the body. The method utilizes accelerated high energy ions, primarily carbon and neon, at the BEVALAC accelerator at the Lawrence Berkeley Laboratory. The research program applied to medicine utilizes heavy-ion radiography for low dose mammography, for treatment planning for cancer patients, and for imaging and accurate densitometry of skeletal structures and brain and spinal neoplasms. The presentation will be illustrated with clinical cases under study. Discussion will include the potential of heavy-ion imaging, and particularly reconstruction tomography, as an adjunct to existing diagnostic imaging procedures in medicine, both for the applications to the diagnosis, management and treatment of clinical cancer in man, but also for the early detection of small soft tissue tumors at low radiation dose.

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Introduction

The basic elements of radiological imaging are image resolution and patient dosage. The ability of x-rays to differentiate among tissues depends on their absorption coefficients; the softer the x-rays, the higher is the absorption coefficient, and the greater the ability to differentiate among structures of similar atomic composition. When soft x-rays are used for diagnostic imaging, a great disadvantage develops, since the higher the absorption coefficients, the greater *is* the absorption of radiant energy in the tissues traversed and the greater the radiation dose to the patient.

When small density differences in tissues exist, sensitive detection of atomic composition can be achieved by using the variation of the stopping power of the tissue to accelerated heavy particles rather than the variation in the x-ray attenuation coefficients.[1-4] This increased resolution derives, in part, from the fact that particle beams have fixed range. For diagnostic x-rays, the radiations must penetrate the entire structure and retain sufficient intensity to expose the radiographic film or detector. For charged particle imaging, on the other hand, all particles traverse the structure, and are utilized in measuring the stopping powers. Heavy-ion radiography affords a sensitivity increase over x-rays, and this is accomplished at a considerable reduction of radiation dose.

The present report provides a brief overview of the development of heavy-ion imaging applied to medicine at the Lawrence Berkeley

Laboratory, and illustrates the potential of heavy particle radiography in the investigation of a number of existing problems in clinical diagnostic roentgenology. These include: (1) the advantage of the significantly higher sensitivity of particle radiographic imaging with much lower patient dosage compared with x-rays (e.g., low-dose heavy-ion mammography); (2) noninvasive diagnostic heavy particle imaging of dynamic structures with subsecond exposures to eliminate motion artefacts (e.g., cardiac heavy-ion radiography); and (3) measurement of residual range for determination of two- and three-dimensional density distribution (e.g., heavy particle computed tomography).

Procedure of heavy-ion radiography

The BEVALAC facility[5-7] at the Lawrence Berkeley Laboratory can accelerate fully stopped atomic nuclei from carbon (Z=6) to krypton (Z=34). Useful ranges in tissue of 40 cm or more are available. Heavy particle radiographic studies to date have been conducted with beams of helium-4, carbon-12, oxygen-16, and neon-20 at several different energies.

When initial studies with heavy-ion beams were begun in 1971, it became apparent that photographic x-ray film could not serve as a satisfactory imaging detector system, since film could only respond to a very limited set of range differences and was subject to large background fluctuations.[2-4] The method of heavy-ion radiography developed in our laboratory overcomes these difficulties by the use of plastic nuclear track detectors originally developed for space research to study heavy primary cosmic rays and to record tracks due to nuclear fission fragments. Figure 1 illustrates schematically the technique of heavy-ion radiography. A nearly parallel monoenergetic beam of heavy particles passes through the object to be radiographed, and stops in a stack of thin plastic nuclear detectors (e.g., Lexan or cellulose nitrate), thereby detecting the exact position and depth of each stopping heavy ion. The particles of sufficiently high LET produce a latent lesion in the plastic foil that can be developed later by the application of concentrated (6.25 N) NaOH to form a microscopic tapered hole. The stopping point distribution in the plastic nuclear detector stack corresponds to the residual range distribution of the particles after crossing the object. Therefore, the plastic stacks indirectly measure the stopping power distribution in the radiographed object.

The information on nuclear detector stack consisting of some 25 to 100 plastic sheets can be viewed qualitatively as a radiograph, or it can be photographed and then viewed. Alternatively, the information on location and residual range can be transferred by an optical scanning method to a computer for analysis and eventual image display.[8-12]

Computer synthesis and image display

The arrangement for the digitization, computer synthesis, and image display process has been described previously.[11] The individual nuclear track detector foil is dark field illuminated and scanned with a Vidicon camera. The signal from the camera is then digitized by a high-speed analog-to-digital converter (or digitizer). The computer is used to calculate the average stopping point at each lateral point (pixel location) for processing and image display. The information contained in the data is the average penetration of the beam into the plastic stack, i.e., the average stopping point z of the particle.

The information in a typical stack of 50 detector sheets, when digitized on a 256 x 256 array into 256 intensity levels, consists of 3.3 megabytes of data. We have used several computer programs developed at the University of San Francisco and the Lawrence Berkeley Laboratory to obtain particle radiographic images using a variety of computers. We are presently developing our programs on the a PDP11-34 and VAX-780 computers. The image is viewed on a RAMTEK display system, and hard-copy gray-tone reproductions are readily obtained.

Resolution

In heavy-ion radiography, the basic elements of the radiological imaging process, viz., radiation dose and resolution (i.e., density or longitudinal, spatial or lateral, and volume or combined depth and area), are a function of the physical interactions between the beam particles and the target, the characteristics of the heavy particle beam, and the type of particle track detector used for imaging. The two most important physical characteristics of heavy-ion beams affecting image resolution and radiation dose are range straggling and multiple coulomb or small-angle scattering.

Density or depth resolution is the resolution for measuring the stopping power of the radiographed object; this depends on the initial energy spread and the range straggling of the charged particles, that is the variation in the ranges of particles with the same incident energy. Range straggling is the dominant limitation in depth resolution in heavy-ion radiography. The magnitude of straggling is nearly proportional to the range and to the the inverse square root to the particle mass. The thicker parts of the human body are equivalent to 30 to 40 cm of water in their stopping power; the range straggling for protons (mass = 1) is about 1.0% of the range; for helium ions (mass = 4) it is about 0.5% or half that for protons; for accelerated carbon ions (mass =12), it is only 0.3% of the range. Thus, carbon-12 ions are about 3.5 times better in the resolution of depth than protons, and 1.7 times better than alpha particles, but this is achieved at the expense of a higher dose.

Spatial or lateral resolution, on the other hand, depends on the deflection of the heavy particles caused by multiple coulomb or small-angle scattering. While very little energy is exchanged in the nuclear interactions between the accelerated particles and the atomic nuclei in the stopping material, the moving particle is deflected from its original direction of travel, usually through a very small angle. The cumulative effect of many of these small deflections is known as multiple scattering of the particles, and is primarily responsible for the lateral distribution of the stopping points. As in the case of range straggling, multiple scattering is strongly dependent on the atomic number of the incident particle, and depends on approximately the inverse 0.6 power of the mass of the particle. For a given particle range, there is a much smaller spread in the lateral positions of the distribution of the stopping points for the heavier charged particles, such as carbon-12, oxygen-16 and neon-20.

Combining depth resolution and lateral (or area) resolution characteristics provides information on volume resolution characteristics to be expected with heavy-ion radiography. Heavy particles are best suited to high depth resolution because they have much smaller values of range straggling than light particles. Lateral resolution is very dependent on the image-processing techniques that are applied to the radiographs. Furthermore, lateral resolution is not independent of depth resolution. However, due to the lateral distribution of stopping points produced by the physical characteristics of multiple small-angle scattering, the lateral resolution appears to be the limiting factor in heavy-particle radiography. However, the theoretical evaluation of depth resolution and lateral resolution lead to the conclusion that heavy particles, such as carbon ions, can resolve substantially smaller volume features than protons.

Compared to diagnostic x-ray imaging, heavy ions such as carbon-12 are much more sensitive to small electron density differences in tissues; thus greater density discrimination is achieved, and can be visualized with higher contrast and significantly lower radiation doses. On the other hand, the lateral resolution of x-rays, that is, in planes perpendicular to the direction of the beam, is better than that achieved by heavy charged particles, and this is due primarily to multiple scattering of charged particles.

Radiation dose

The factors that affect the radiation dose of heavy ions include the particle energy loss rate, the particle fluence or particles per unit area, the magnitude of range straggling, and nuclear disintegrations. Since reasonably low initial energies are used in heavy-ion radiography, and the radiation dose of interest is at a point somewhat removed from the stopping point of the particles, only the factors concerned with particle energy loss and the particle fluence need to be known to obtain a reasonably accurate evaluation of dose absorbed. The deposited energy density of heavy ions in MeV/cm^3 is given by the product of the particle fluence and the LET; this is readily converted to rads. The dose increases with increasing atomic number, but even with the heaviest ion studied, argon-40, for a particle fluence of 1000 particles per cm^2, at 1 cm in water, the dose is quite low. For carbon-12 at 30 cm of water (the thickness of the chest), the dose per 1000 particles per cm^2 is about 10 mrad.[3,4] The total number of particles in a beam remains quite low, even if large radiographs are made. For example, a 50 cm x 50 cm carbon-ion radiograph, with 1000 particles per cm^2, uses only about 2.5×10^6 particles. This is several orders of magnitude lower than the maximum available from the BEVALAC in a single pulse.

Applications to medicine

Our laboratory has been carrying out extensive studies on the physical and biological aspects of heavy-ion radiography.[1,3,4,10-12,14] Considerable work has been done on the physical and accelerator beam aspects of particle radiography,[5-7] on detector characteristics and response,[2,8,15] on image resolution and radiation dose,[1,2,9] computer analysis and image display,[9,13] and two- and three-dimensional reconstruction.[9,11,13] Early phantom studies for the imaging of tissues and organs were begun in 1974, and tissue specimen radiography (particularly the examination of normal human tissues and tissues bearing a variety of tumors) followed soon thereafter. Heavy-ion radiography with human patients was initiated in 1976 with low-dose mammography,[16] and later in that year, radiography of soft tissue abnormalities was begun. The following is a brief overview of our studies with humans, and will illustrate the application of heavy-ion radiography to mammography, musculoskeletal radiography, and computerized tomography.

Mammography

Following the recommendation of the National Cancer Institute, the first clinical trial of heavy-ion mammography was begun in June 1976. In the first three years since the initiation of the clinical diagnostic program, significant advances have been achieved.[10,12,16] For the examination, the patient lies on a specially designed stretcher; the breast to be radiographed is immersed in a vessel with parallel walls filled with water at 37°C. A single beam pulse is used, e.g., carbon-12, 250 MeV/amu, fluence of 1000 particles per cm^2. A 50 to 100 mrem dose to the breast is sufficient to obtain a stack of 25 to 50 plastic films with a wealth of quantitative data. In the clinical trial, some 35 patients with previously diagnosed breast tumors or previous breast biopsies have been radiographed.

A comprehensive study is in progress. The important findings of the initial patient clinical trials are as follows:

1. Heavy-ion mammorgraphy is a low-dose, safe, reliable, and noninvasive imaging procedure which provides an enormous amount of quantitative information for image processing, analysis, and image display in every patient examined.[16]

2. The heavy-ion radiation dose to the breast is approximately 1/25th to 1/250th of that in conventional x-ray mammography or xeroradiography. Doses of about 50 mrad for carbon-ion radiographs routinely provide images of high quality, and diagnostic images can be obtained with a dose of only 10 mrad. It is not yet established whether a dose of 10 to 20 mrad for carbon-ion mammography will

produce reliable image quality (Figure 2.) These doses remain substantially less than x-ray mammography and xeromammography, and the x-ray methods do not provide the capability of computer anaysis and display, of quantitative density profiles, and other information available for determination of anatomical composition of normal and diseased breast tissues.

3. In all patients examined, whenever x-ray mammography detected abnormal densities within breast tissue, the carbon-ion radiographs demonstrated the same abnormal density as well. However, carbon-ion radiographs provide a greater sensitivity for detecting minute contrasting tissue densities in the breast than do x-ray methods. X-rays provide improved lateral resolution in images, and are relatively more sensitive to higher atomic number structures, such as microcalcifications in the breast (Figure 3).

4. On the other hand, the carbon-ion radiographs demonstrated abnormal densities in the breasts of two patients which were not detected by x-ray mammography. These proved to be nonpalpable masses, lying deep in the breast, and measuring less than 1 cm on the heavy-ion images (Figure 4). In other words, in the initial clinical trials of patients with potentially detectable disease, carbon-ion mammography demonstrated small (less than 1 cm) soft-tissue breast cancers which were not demonstrable with conventional x-ray mammography.

5. Heavy-ion mammography detected changes in tissue structure detail in dense breast tissue more readily than x-rays. Heavy-ions may have an advantage in imaging dense breasts with fibrocystic disease.

6. Heavy-ion mammography provides information in the form of graytone integrated images, isodensity contour plots, tissue stopping power distribution profiles, and perspective density contours that represent differing quantitative image display methods which provide valuable diagnostic information on the internal anatomical pathological internal structure of normal, diseased, and particularly neoplastic breast tissue in patients of all ages.

Musculoskeletal radiography

The initial study of heavy-ion radiography of the musculoskeletal system consisted of exposure of a human foot amputated because of ischemic vascular disease.[12,14] Superior resolution of structures differing little in density was achieved with heavy-ions compared with x-rays; lateral resolution was less, and the edges of the anatomic structures were less well defined. The degraded image on the heavy-ion radiograph was the result of the lower spatial resolution and of the relatively low flux rate of heavy ions causing quantum mottling.[4,10,12] Carbon-ion radiography demonstrated the Achilles tendon, flexor and extensor tendons, and areolar and adipose tissues between tendons, muscles and bones, which could not be seen on x-ray radiography, although osseous structures imaged on the x-ray radiograph were better defined.

A number of computer analysis and display methods of integrated heavy-ion images provide clinically useful image representations in forms which can prove meaningful to the radiologist. This was illustrated in a neon-ion radiograph of the leg of a patient with a painful neurofibrous mass surrounding the peripheral nerve of the lower limb. The low density tumor was identified on the heavy-ion radiograph, but could not be imaged with conventional or magnification x-rays or CT images of the leg. In the heavy-ion radiograph, the average particle stopping point at each lateral position is mapped into a gray level on the image. Oblique illumination plots, perspective views, and isodensity contour plots represent various forms of image representation which provide important quantitative information. In the limbs, density distribution plots provide quantitative "peaks" of structural tissue density in bone, fat, tendons, and muscles.

Cardiac heavy-ion radiography

The potential of heavy-ion radiography for the study of cardiac disease in humans is being studied in our laboratory. The potential exists for differentiating between normal myocardium, the ischemic myocardium, the scarred myocardium, and blood in the chambers of the heart. True three-dimensional heavy-ion reconstruction of the heart is feasible in principle with a beam pulse in the subsecond range. Therefore, our initial studies of heavy-ion imaging of the heart are directed toward accurate detection and sizing of the infracted myocardium, which remain problems of major clinical importance.

We have succeeded in obtaining a neon-ion radiographic image of the cardiac structures in the thorax of the living dog (Figure 5). The cardiac silhouette, the great vessels of the mediastinum, and the adjacent vertebral column, muscles, fat, and skin are readily identified. In the heart, the right ventricle, the aortic arch and the dense ventricle myocardial muscle mass can be seen. The density in the thin-walled area lying posteriorly has the contour of the cardiac chamber. We are presently analyzing the digitized data, and are determining the stopping power values of the various cardiovascular structures.

Heavy-ion computer tomography

Heavy-ion radiography has proved to be very suitable for two-dimensional image reconstruction by methods of computerized tomography.[11] Because the passing or stopping of all individual heavy particles are recorded, and the sensitivity for stopping power measurements is high, image reconstructions of high quality are being obtained at relatively low radiation doses. The method of heavy-ion computerized tomography is in its initial stages, but successful reconstructions of a rat head and a human spine have been achieved; and reconstruction of the human brain and of the human fetus are presently being accomplished.

The technique for two-dimensional reconstruction for heavy particle computed tomography has been described by Holley et al.[11] The heavy-ion beam is passed through a narrow slit; as subsequent beam pulses are arriving, the patient or specimen is rotated to different angles of incidence while the nuclear plastic detector stack is moved vertically between beam pulses. The images formed in the stack by a sequence of beam pulses appear as narrow bands at specified angles of incidence and do not overlap.

The initial trial of two-dimensional reconstruction of a biological object was a carbon-ion reconstruction of a transverse section of a rat's head fixed in formalin.[12] The head was mounted in a specially constructed specimen rotating unit. The beam pulse rate at the Bevatron was 12 pulses/minute, the range of the carbon particles was approximately 12 cm of water; the head was rotated on a vertical axis, 3 degrees between exposures, and 60 views were taken. It required several minutes to obtain sufficient data for reconstruction.

Both the soft tissues and bone structures can be seen with rather high resolution (Figure 6). The structures of the skull and face are prominently displayed. the nasopharynx and oropharynx, the posterior walls of the orbits superimposed on the petrous and frontal bones, the mandible, the soft muscular tissues of the cheeks, and the submandibular tissues are identified. The petrous temporal bone complex can be seen, and demonstrates some external and middle ear structures. The density resolution of the carbon beam is good; the lateral resolution is better than 0.1 cm.

We have accomplished the first carbon-ion CT reconstruction of the human spine and spinal cord, using a 15-cm section of a cadaver lumbar spine en bloc, and have demonstrated high resolution of soft tissues and osseous structures in a 2-mm section, including the vertebra, the spinal cord, the paraspinous muscles, fascia, the aorta, and the overlying skin and subcutaneous fat of the back. These studies are continuing; we are presently analyzing carbon-ion reconstruction scans of the adult human brain, and have applied the method to the fetal head and abdomen.

Conclusions

This brief overview of our research in heavy-ion radiography at the Lawrence Berkeley Laboratory only introduces a limited number of the potential applications in medicine. Heavy-ion radiography is a newly developed noninvasive low dose imaging procedure which provides increased resolution of minute density differences in soft tissues of the body. The method utilizes accelerated high energy charged particles, e.g. carbon and neon ions, at the BEVALAC accelerator. The investigative program is directed primarily to the development of safe and reliable noninvasive diagnostic imaging procedures for mammography with very low radiation doses, for imaging and accurate densitometry of the musculoskeletal system and the brain and spinal cord, and for imaging the moving heart. The potential of heavy-ion radiography, and particularly two- and three-dimensional reconstruction tomography as an adjunct to existing diagnostic imaging procedures is great, both for the applications to diagnosis and management of cancer, neurological and cardiovascular disease in man, and particularly for the early detection of small, soft tissue neoplasms at low radiation dose.

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Figure Captions

Figure 1. Heavy-ion radiography using plastic nuclear track detectors. The particle beam passes through the tissue and the particles are recorded at their stopping points in the plastic detector stack. The distribution of etched tracks in the detector sheets form the radiographic image.

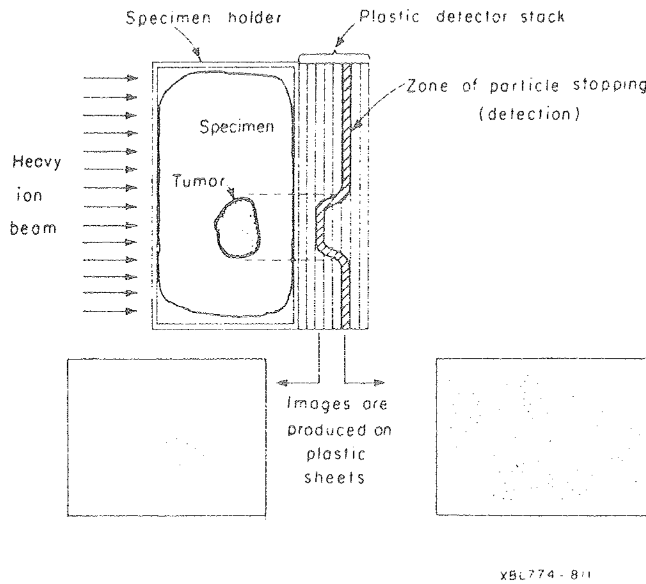
Figure 2. Carbon-ion radiograph, single nuclear track detector sheets, of the breast; reliable image quality on mammography is achieved at a breast dose of 20 mrad (left), and is only slightly improved at a dose of 60 mrad (right).

Figure 3. X-ray mammography (left) and carbon-ion mammography (right); the heavy-ion radiograph is a single nuclear track detector sheet and indicates the stopping point distribution of the charged particles.

Figure 4. Carbon-ion mammography: small, soft tissue breast cancer not demonstrated with conventional x-ray mammograph; left, normal breast; right, nonpalpable cancer nodule (arrow).

Figure 5. Neon-ion radiographic image of the chest of a living dog; the cardiac structures great vessels of the mediastinum, lungs, vertebral column, muscles, fat, and skin are identified.

Figure 6. Carbon-ion CT reconstruction of coronal section of a rat head.



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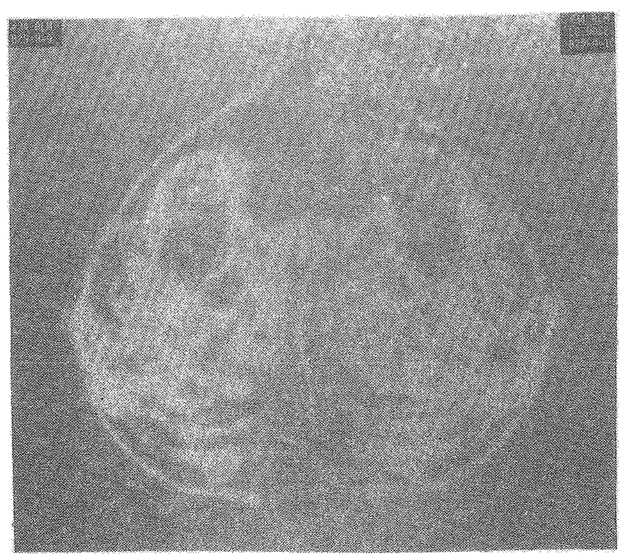

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Figure 2. Carbon-ion radiograph, single nuclear track detector sheets, of the breast; reliable image quality on mammography is achieved at a breast dose of 20 mrad (left), and is only slightly improved at a dose of 60 mrad (right).

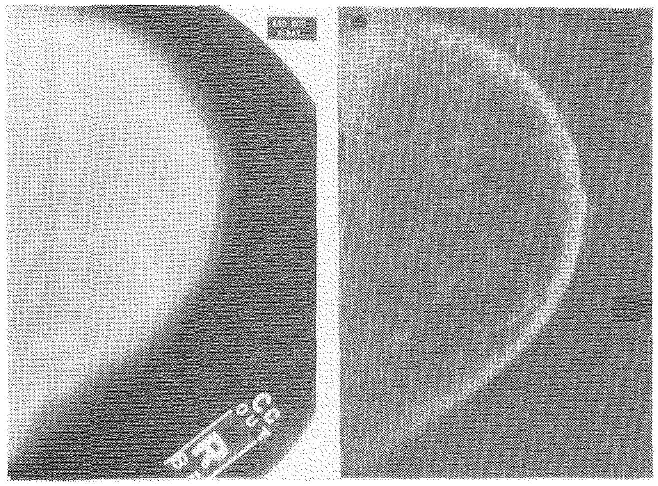

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Figure 3. X-ray mammography (left) and carbon-ion mammography (right); the heavy-ion radiograph is a single nuclear track detector sheet and indicates the stopping point distribution of the charged particles.

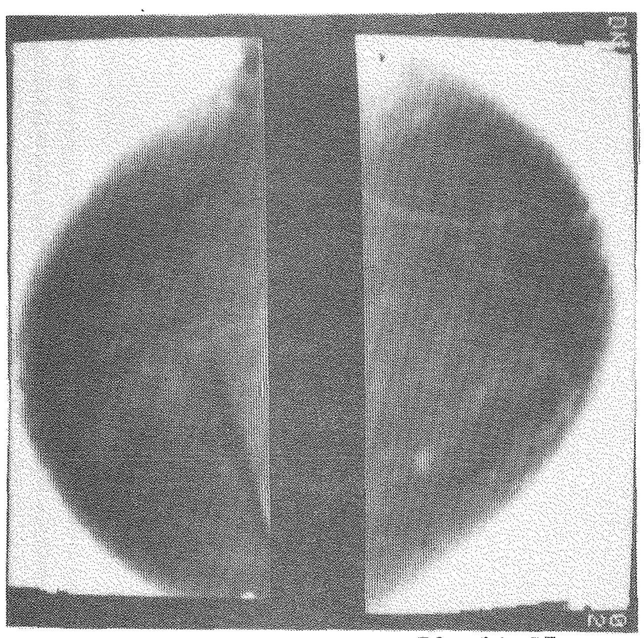

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Figure 4. Carbon-ion mammography: small, soft tissue breast cancer not demonstrated with conventional x-ray mammograph; left, normal breast; right, nonpalpable cancer nodule (arrow).

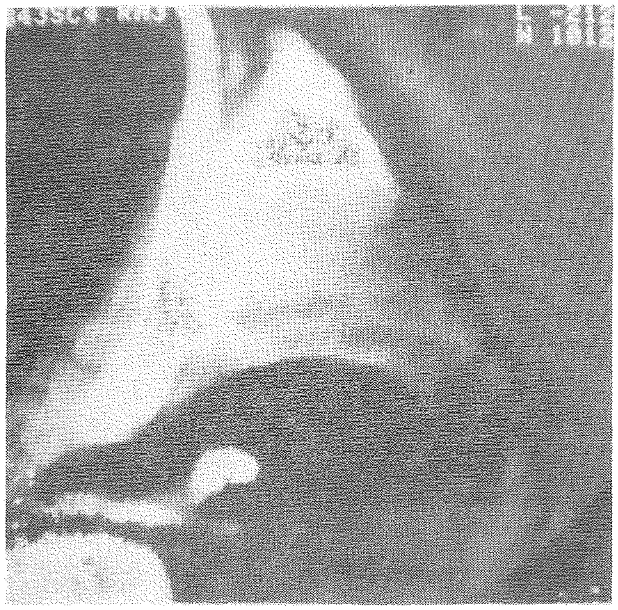

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Figure 5. Neon-ion radiographic image of the chest of a living dog; the cardiac structures great vessels of the mediastinum, lungs, vertebral column, muscles, fat, and skin are identified.

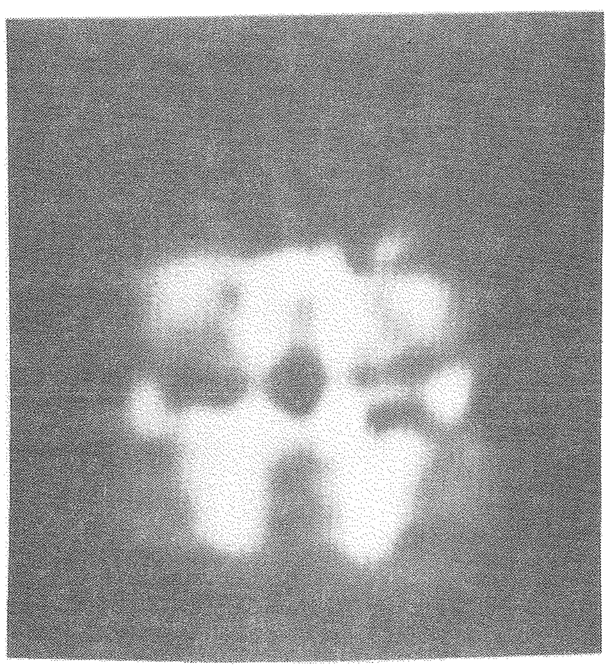

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Figure 6. Carbon-ion CT reconstruction of coronal section of a rat head.